Sustained reduction in severe hypoglycemia in adults with type 1 diabetes complicated by impaired awareness of hypoglycemia: 2-year follow-up in the HypoCOMPaSS randomized clinical trial

Running title: Sustained reduction in severe hypoglycemia

Authors

Stuart A Little MRCP[1*], Jane Speight PhD[2,3,4*], Lalantha Leelarathna PhD[5], Emma Walkinshaw MRCP[6], Horng Kai Tan MRCP[7], Anita Bowes MSc[8], Alexandra Lubina-Solomon MRCP[6], Thomas J Chadwick PhD[9], Deborah D Stocken PhD[9], Catherine Brennand[10], Sally M Marshall FRCP[1], Ruth Wood MSc[10], David Kerr FRCP[8], Daniel Flanagan FRCP[7], Simon R Heller FRCP[6], Mark L Evans FRCP[5], James AM Shaw FRCP[1]

Affiliations

1. Institute of Cellular Medicine, Newcastle University, Newcastle, UK.
2. School of Psychology, Deakin University, Geelong, Victoria, Australia.
3. The Australian Centre for Behavioural Research in Diabetes, Diabetes Victoria, Melbourne, Australia.
4. AHP Research, Hornchurch, UK.
5. Wellcome Trust-MRC Institute of Metabolic Science Metabolic Research Laboratories, University of Cambridge, UK.
6. School of Medicine and Biomedical Sciences, Sheffield University, UK.
7. Peninsula College of Medicine and Dentistry, Plymouth, UK.
8. Centre for Postgraduate Medical Research and Education, Bournemouth University, UK.
9. Institute of Health and Society, Newcastle University, Newcastle, UK.
10. Newcastle Clinical Trials Unit, Faculty of Medical Sciences, Newcastle University, Newcastle, UK.

*These authors contributed equally to the work

Correspondence to:

James Shaw
Professor of Regenerative Medicine for Diabetes and Honorary Consultant Physician
Diabetes Research Group, Institute of Cellular Medicine
4th Floor William Leech Building
The Medical School, Newcastle University
Framlington Place
Newcastle upon Tyne NE2 4HH, UK
Email: jim.shaw@ncl.ac.uk; Telephone: +44 (0)191 208 8129

Word count: 4000 (inc Abstract). 2 Tables; 1 Figure

Abstract

Objective

Severe hypoglycemia is a feared complication of type 1 diabetes yet few trials have targeted prevention using optimized self-management (educational, therapeutic and technological support). We aimed to investigate whether improved awareness and reduced severe hypoglycemia, achieved during an intensive RCT, were sustained following return to routine care.

Research Design and Methods

96 adults with type 1 diabetes (29±12 years duration) and impaired awareness of hypoglycemia at five UK tertiary-referral diabetes centers were recruited into a 24-week 2x2 factorial RCT (HypoCOMPaSS). Participants were randomized to: pump (CSII) or multiple daily injections (MDI); and real-time continuous glucose monitoring (RT-CGM) or self-monitoring of blood glucose (SMBG); with equal education/attention to all groups. At 24 weeks, participants returned to routine care with follow-up until 24 months, including free choice of MDI/CSII; RT-CGM vs SMBG comparison continued to 24 months. Primary outcome was mean difference (baseline to 24 months; between groups) in hypoglycemia awareness.

Results

Improvement in hypoglycemia awareness was sustained (baseline Gold score: 5.1±1.1; 24m: 3.7±1.9; $p<0.0001$). Severe hypoglycemia rate was reduced from 8.9±12.8 episodes/person-year over the 12 months pre-study to 0.4±0.8 over 24 months ($p<0.0001$). HbA1c improved (baseline: 8.2±3.2% (66±12mmol/mol); 24m: 7.7±3.1% (61±10mmol/mol); $p=0.003$). Improvement in treatment satisfaction and reduced fear of hypoglycemia were sustained. There were no significant differences between interventions at 24 months.

Conclusions

Optimized insulin replacement and glucose-monitoring underpinned by hypoglycemia-focused structured education should be provided to all with type 1 diabetes complicated by impaired awareness of hypoglycemia.

Hypoglycemia is one of the most feared complications of type 1 diabetes (1), as it can result in collapse, coma, seizures, injury and, in rare instances, sudden death. One in five adults with type 1 diabetes have experienced severe hypoglycemia (requiring assistance for recovery (2)) in the previous six months, regardless of overall glycemic control (3). Around half of those with type 1 diabetes for at least 15 years experience an episode each year (4). Severe hypoglycemia is six-fold more common in those with impaired awareness of hypoglycemia (5), which affects 20-25% of adults with type 1 diabetes (3, 6), rising to almost 50% after 25 years (1).

Randomized clinical trials (RCTs) of continuous subcutaneous insulin infusion (CSII) pump therapy and continuous glucose monitoring (CGM) have demonstrated that technological approaches can help prevent severe hypoglycemia (7, 8), albeit without improving awareness of hypoglycemia. However, studies are short-term (typically 6 months) and it is unclear how much of the observed benefit is due to increased education/attention provided alongside the active technological intervention. Indeed, much of the evidence to date for sustained reduction (at least one year) in severe hypoglycemia and restoration of hypoglycemia awareness comes from studies investigating the impact of structured type 1 diabetes education (9) or targeted hypoglycemia-focused psycho-educational intervention (10, 11).

In the 24-week HypoCOMPaSS RCT, we demonstrated that improved hypoglycemia awareness and prevention of recurrent severe hypoglycemia is possible in a high-risk population of adults with long-standing type 1 diabetes without worsening overall glycemic control (12). We compared insulin pumps (CSII) with multiple daily injections (MDI); and adjuvant real-time continuous glucose monitoring (RT-CGM) with conventional self-monitoring of blood glucose (SMBG) – importantly, with equal education/attention for all groups irrespective of randomization. We found no difference in outcomes at 24 weeks by insulin delivery or glucose monitoring modality.

Following 24-week RCT completion, participants returned to routine clinical care with 6-monthly data collection until 24 months. While participants were able to change insulin delivery modality at 24 weeks, the RT-CGM vs SMBG randomized comparison continued to 24 months. Our aim in the current study was to determine whether the improved awareness and prevention of recurrent severe hypoglycemia previously seen across all intervention groups at 24 weeks was sustained to 24 months.

Research Design and Methods

Study design and participants

We have reported elsewhere the study protocol (13) and 24-week RCT results (12). The protocol (13) was approved by a central Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency, with independently-chaired Trial Steering Committee and Data Monitoring and Ethics Committee oversight. All participants provided written informed consent.

In summary, HypoCOMPaSS was a multicenter, 24-week, 2x2 factorial study at five UK tertiary referral diabetes centers providing structured education in type 1 diabetes with specialist expertise in the management of hypoglycemia and the use of CSII/RT-CGM technologies. Eligible participants were aged 18-74 years with C-peptide-negative type 1 diabetes and impaired awareness of hypoglycemia, confirmed by Gold score ≥4 (6).

In addition to previously documented baseline and 24-week visits, all participants were asked to return at 12, 18 and 24 months for data collection. Participants prospectively recorded episodes of severe hypoglycemia. Before each visit, participants underwent 7 days' blinded CGM (Medtronic iPRO).

Randomisation and masking

Using a web-based system, and stratified by baseline HbA1c (< and ≥8% (64 mmol/mol)) and by center, participants were allocated randomly on an equal allocation basis to one of four groups: MDI (insulin aspart/glargine) with SMBG; MDI with SMBG and RT-CGM; CSII (insulin aspart) with SMBG; CSII with SMBG and RT-CGM. Allocation sequence was generated by an individual not otherwise involved in participant recruitment. Neither participants nor investigators were blind to study allocation.

Procedures

After baseline assessment, all participants attended a brief (1-2 hour), education session in small groups or one-to-one, guided by a standardized workbook (13) . In summary, the aim was to facilitate reflection on personalized factors associated with dangerous hypoglycemia with formulation of individualized plans to prevent further significant events while maintaining overall glycemic control. The session was structured around the four points (N, E, S, W) of *'my hypo compass'* to: *Never* delay hypoglycemia treatment; establish times of *Extra* risk; recognise *Subtle* hypoglycemia symptoms; and be *Wary* about detecting and

preventing nocturnal hypoglycemia. Beyond this session, all participants received equivalent support including 4-weekly follow-up visits throughout the RCT.

At the end of the 24-week RCT, participants returned to routine clinical care without further study-related attention/support beyond 6-monthly data collection. All had the option of switching insulin delivery modality within the context of UK clinical guidance, given confirmed problematic hypoglycemia at baseline (14). Decision to change insulin delivery modality was not dictated by study design or influenced by study investigators. Those randomized to RT-CGM continued to be provided with sensors providing the potential for uninterrupted use for a further 18 months (24 months in total). Those randomized to SMBG continued without access to RT-CGM.

Outcomes

All RCT outcome measures have been reported in detail elsewhere (13). The primary outcome was difference (between baseline and 24 months, and between randomized groups) in hypoglycemia awareness determined by Gold score (6).

Pre-specified secondary outcomes were differences (as above) in hypoglycemia awareness (assessed by Clarke questionnaire (15) and HypoA-Q Impaired Awareness scale score) (16); severe hypoglycemia rate and proportion affected; biochemical hypoglycemia (identified by blinded CGM profile: percentage time with glucose $\leq$3 mmol/l); overall glycemic control (HbA1c); total daily insulin dose, body weight; and patient-reported outcomes, primarily fear of hypoglycemia (Hypoglycemia Fear Survey II: HFS-II) (17) and satisfaction with diabetes treatment (Diabetes Treatment Satisfaction Questionnaire: DTSQ) (18).

Safety endpoints were hospital admissions, diabetic ketoacidosis and infections related to insulin delivery and glucose sensor sites.

Follow-up for all primary and secondary outcome measures was planned to 24-months post-randomization.

Statistical analysis

The primary trial comparison was CSII vs MDI and RT-CGM vs SMBG alone, as reported elsewhere (12). Long-term analyses were based on pre-planned secondary outcomes at 24-month follow-up in addition to changes between baseline and 24 months in the overall study population. Per-protocol analyses were planned based on knowledge of participant behavior and undertaken for insulin delivery modality, given that participants had freedom to choose

after the 24-week RCT (MDI only throughout, switched with use of both MDI and CSII over the 24 months, or CSII only throughout) and for RT-CGM use (<50 versus ≥50% of days in study). Data analysis took the form of a complete case analysis. Missing data were not deemed sufficient to justify imputation of values. Secondary long-term outcome analyses were exploratory, based mainly on descriptive and graphical representations. Hypothesis testing for the primary comparison was pre-planned, with significance levels set at $\alpha=0.05$ throughout. Data are presented as mean±SD or proportions. 24-month data were analysed using t-test or Chi-Square. Statistical analysis was undertaken using STATA (versions 12 & 14).

Role of the funding source

Neither Diabetes UK nor the providers of study devices had any role in study design, data collection, analysis, interpretation, writing, or in the decision to submit for publication.

Results

Participants

Ninety-six adults with type 1 diabetes and impaired awareness of hypoglycemia were randomized. At baseline, mean±SD age was 49±12 years and diabetes duration 29±12 years, 35 (36%) were men, 97% were using MDI (3% using CSII), and none had previously used RT-CGM. Full demographic and clinical characteristics were similar in all groups, published previously (12).

At 24 months, 76 (79%) were retained (Supplemental Figure 1). Baseline characteristics in those lost to follow-up were comparable to those retained for the study duration (Table 1). Thirty-nine (78%) participants randomized to MDI were retained at 24 months, with 10 (26%) still using MDI. Thirty-seven (80%) participants randomized to CSII were retained, with 25 (68%) still using CSII. Thirty-nine (81%) participants randomized to SMBG alone were retained at 24 months, and all were still using SMBG alone as commencement of RT-CGM during study follow-up was precluded. Thirty-seven (77%) participants randomized to RT-CGM plus SMBG were retained, with 11 (30%) still using RT-CGM at study completion.

Long-term outcomes

The improvement in hypoglycemia awareness attained during the RCT irrespective of randomized intervention (12) was sustained in the overall study population throughout the post-RCT follow-up (Table 2). Maintained benefit at 24 months was confirmed by significant

reductions in Gold, Clarke and HypoA-Q Impaired Awareness scale scores compared to pre-intervention baseline. In parallel, the significantly reduced rate of severe hypoglycemia attained during the RCT was sustained during long-term follow-up, with ≤20% of participants experiencing events over each 6-month period (Table 2).

Comparing severe hypoglycemia over the 24-month follow-up with the 12-month period prior to randomization confirmed a 95% reduction in annualized rate from 8.9±12.8 to 0.4±0.8 episodes per person-year ($p<0.0001$) (Figure 1). Over the 24-month follow-up, 36% of participants were affected versus 92% over the 12 months pre-study. All who experienced severe hypoglycemia events during the study had reported severe hypoglycemia within the 12 months pre-study. In those who experienced severe hypoglycemia over the 24-month follow-up, annualized rate was reduced to 1.5±1.0 episodes per person-year. Only five (5%) participants experienced >2 severe hypoglycemic events/person-year, compared with 56 (58%) over the 12 months pre-study. Comparing consequences of severe hypoglycemia over the 24-month follow-up with the 12 months pre-study: 8% vs 32% of participants required glucagon administration 7% vs 33% paramedic assistance and 2% vs 6% hospital attendance/admission.

HbA1c at 24 months was significantly lower than at baseline (Table 2). In participants with baseline HbA1c ≥8% (64 mmol/mol), glycemic control improved incrementally throughout the 24-month study period, while in those with baseline HbA1c <8%, glycemic control was not 'relaxed', with average remaining <7.5% (58 mmol/mol) (Figure 1).

Previously observed improvements in treatment satisfaction, perceived frequency of hypoglycemia and hyperglycemia, and fear of hypoglycemia were sustained throughout the 24-month study (Table 2).

Although the reduction in clinically important (19) biochemical hypoglycemia (interstitial glucose ≤3 mmol/L) achieved in the RCT (Baseline: 53±63 min/24 h vs 24 weeks: 24±56 min/24 h) was maintained throughout post-RCT follow-up (Table 2), this was no longer statistically significant at 24 months (37±56 min/24h). The significant reduction in mean total daily insulin dose seen within the RCT, equating to 8 units per participant, was sustained at 24 months with weight unchanged throughout the study (Table 2).

Insulin delivery comparison

At 24 months, there was no significant difference in hypoglycemia awareness between those initially randomized to CSII and those to MDI (Supplemental Table 1). Reductions in severe

hypoglycemia, HbA1c, daily insulin dose and other secondary endpoints were all equivalent in the MDI versus CSII group intention-to-treat analysis.

Having completed the primary 24-week RCT on randomized intervention, participants were free to change insulin delivery modality supported by their clinical team on return to routine care without any further study-specific support. Nevertheless, all participants remained in specialist centers and those transitioning to CSII received additional training and support according to established center-specific practice. Per-protocol analysis confirmed comparable outcomes in those who used both MDI and CSII over the 2-year study period to those using only MDI or CSII (Supplemental Table 1). The greater satisfaction with treatment (DTSQ total) observed with CSII compared to MDI at 24 weeks was no longer apparent at 24 months (Supplemental Table 2). Although statistical analyses were not deemed appropriate due to low numbers, possible associations were seen between improved hypoglycemia awareness, reduced severe hypoglycemia and lower hypoglycemia worry in those choosing to remain on MDI throughout. Higher HbA1c in those who remained on MDI was also noted (Supplemental Table 2).

Monitoring regimen comparison

At 24 months, there were no significant differences between those randomized to SMBG alone and those to RT-CGM, in terms of hypoglycemia awareness, severe hypoglycemia or any secondary outcomes (Supplemental Table 1).

Despite provision of sensors for uninterrupted RT-CGM use, only 11 (30%) of the RT-CGM group continued to use this technology throughout the full 24-month follow-up. Exploratory per-protocol analysis of the 14 participants with complete RT-CGM usage data compared those using RT-CGM <50% versus ≥50% of the time (Supplemental Table 2). Although small numbers precluded statistical analysis, there were no severe hypoglycemic events and a trend towards improved hypoglycemia awareness observed in those using RT-CGM <50% of the time. As in the primary RCT, higher RT-CGM use was associated with a trend towards less biochemical hypoglycemia.

Comparing outcomes between all participants (Table 2), those randomized to RT-CGM (Supplemental Table 1) and the sub-group who used this monitoring modality throughout the study (Supplemental Table 2) suggests no differences between groups, with the exception of fear of hypoglycemia, which appears particularly low in those who used RT-CGM throughout the 24 months.

Safety

Over the 24-month study, six episodes of ketoacidosis required hospitalisation, five during CSII and one during MDI. All resolved without sequelae. Twelve other severe adverse events (CSII: n=7; MDI: n=5) were unrelated to trial interventions. These included episodes of acute-angle closure glaucoma, pneumonia, gastroenteritis, fractured radius and pre-existing neuropathic foot ulceration requiring intravenous antibiotics.

Conclusions

Improved hypoglycemia awareness and reduced rate of severe hypoglycemia observed in a short-term intensive RCT was maintained at 24 months after return to routine clinical care. This was paralleled by a clinically meaningful 0.5% reduction in mean HbA1c, sustained improvement in treatment satisfaction and reduced fear of hypoglycemia. This study demonstrates that a brief educational intervention with intensive support over 24 weeks leads to benefits sustained over 24 months in a high-risk cohort with long-standing type 1 diabetes and impaired awareness of hypoglycemia. It confirms that avoiding severe hypoglycemia does not need to be achieved at the expense of higher overall glucose levels.

HypoCOMPaSS provides further evidence that structured education and support should underpin interventions targeting impaired awareness of hypoglycemia in type 1 diabetes. This corroborates a meta-analysis concluding that structured education reduces rates of severe hypoglycemia (20). Most previous studies have adopted a before-and-after design with small numbers and short-term follow-up. Only two RCTs with at least 12-month follow-up have specifically recruited participants with impaired awareness of hypoglycemia. In both the HyPOS and HAATT studies (10, 21), reduction in severe hypoglycemia was greater, over 18 and 31 months respectively, in those who received the psycho-educational program than in the control group. Unlike HypoCOMPaSS, neither reported improved HbA1c. It is striking that substantial reductions in total daily insulin dose were observed throughout the current 24-month study without any protocol-driven insulin dose titration regimen beyond the 24-week RCT.

Participants had completed standardized type 1 diabetes education in insulin dose adjustment according to glucose levels and carbohydrate intake prior to study recruitment and all received the *'my hypo compass'* psycho-educational intervention prior to randomization. The absence of a group not receiving hypoglycemia-focused structured education is a limitation, discussed previously (12), although the durability of the impact in this high-risk group prone

to recurrent severe hypoglycemia is reassuring. Sustained effective behavior change enabled through a short-term psycho-educational intervention, despite withdrawal of trial-specific input at 24 weeks, supports cost-effectiveness for wider implementation although formal health economic analysis was not undertaken. An important caveat is that all participants remained under specialist care, in keeping with national guidance recommending this for those with a history of problematic hypoglycemia (22). A qualitative process evaluation is underway to explore facilitators of long-term benefit, in addition to a further RCT comparing standard medical management of impaired awareness of hypoglycemia with and without the '*my hypo compass'* psycho-educational program.

Although previous studies have reported lower severe hypoglycemia rates with CSII compared to MDI (23), only the current RCT has provided equivalent education, attention/support to both groups in addition to optimized basal analog MDI. As all participants fulfilled national criteria for pump therapy (24) at study recruitment, those randomized to MDI were aware that they could switch to CSII at the end of the 24 week RCT and 57% did so supported by their usual clinical team. In parallel, 30% of those randomized to CSII switched to MDI. This crossover (anticipated and supported by the study protocol) occurred despite the RCT demonstrating no differences in biomedical outcomes, fear or perceived frequency of hypoglycemia between insulin interventions. At 6 months, satisfaction with treatment had been higher in those randomized to pump but was comparable at 24 months, after 18 months of preferred insulin delivery. This is consistent with the overall findings that benefits comparable to CSII (including treatment satisfaction) can be achieved in individuals favoring MDI. A trend towards lowest mean HbA1c in those using CSII throughout was seen, although numbers remaining on MDI were small. Recently, the REPOSE trial reported comparable biomedical benefits for those randomized to CSII or MDI with equivalent structured education and attention/support (25). While supporting the conclusion that sustained benefits can be achieved in long-standing type 1 diabetes complicated by impaired awareness of hypoglycemia regardless of chosen insulin delivery modality, the *a priori,* pragmatic decision to allow cross-over after 24 weeks in HypoCOMPaSS was a potential limitation, as it precluded definitive RCT comparison of MDI versus CSII over the full 24-month follow-up period. Further work is needed to establish the relative benefits of CSII over optimized MDI and individual participant drivers to switch from MDI to CSII and *vice versa* during the post-RCT follow-up are being explored through the qualitative process evaluation noted above.

In the current 24-month randomized comparison of SMBG with RT-CGM, both interventions were equally effective in restoring hypoglycemia awareness and preventing severe hypoglycemia without compromising average glycemic control. This may reflect the specific focus on augmenting conventional finger-prick glucose monitoring with targeted post-prandial and 4am testing, in contrast to standard clinical practice (26). It is important to note that, although at 24 weeks in the HypoCOMPaSS study >95% of participants were using low-glucose alerts and 75% stated that RT-CGM was beneficial in preventing severe hypoglycemia, more than two thirds were no longer using this modality at 24 months. This is a limitation as previous trials have reported higher sensor use, together with an association between greater use and optimal impact (26, 27). Mirroring the current study, decreased use and discontinuation over time has been a concern in the non-trial community setting, with >40% of RT-CGM users on enrolment to the US T1D Exchange Clinic Registry having stopped using the technology 12 months later (28). Discomfort wearing and difficulties inserting sensors were the commonest reasons for cessation. Ongoing improvements in reliability and accuracy have been associated with greater use (27, 29). The factors underlying cessation of RT-CGM in HypoCOMPaSS are being further investigated through qualitative analysis of participant semi-structured interviews.

Relatively few participants used RT-CGM ≥50% of the time, but 38% of these continued to experience severe hypoglycemia, whereas none of those using RT-CGM <50% of the time experienced any events. It may be that those at highest risk of severe hypoglycemia are those who used RT-CGM virtually uninterrupted as a 'lifeline' to provide 'technological hypoglycaemia awareness' (20).

Median sensor use of nearly 90% was attained in a recent 16-week crossover trial evaluating RT-CGM in 52 participants with type 1 diabetes and impaired awareness of hypoglycemia on MDI or CSII therapy (30). Biochemical hypoglycemia and number of severe hypoglycemia events was lower during the RT-CGM period. This was associated with reduced fear of hypoglycemia, a possible association with continued RT-CGM in the current study.

Using subcutaneous sensor-based 'flash glucose monitoring' (where readings over the preceding 8 hours are obtained by bringing a reader in close proximity to the sensor), significant reduction in biochemical hypoglycemia has been achieved in an RCT comparison with conventional SMBG among adults with type 1 diabetes and optimal HbA1c (≤7.5%) (31). High participant satisfaction and system utilization (>90%) was reported, though time with glucose <3.1 mmol/L remained substantial even in the intervention arm (3.3%).

Participants with ‘diagnosed hypoglycemia unawareness’ were excluded from the trial and there was no reduction in fear of hypoglycemia. An 8 week pilot RCT comparing RT-CGM with flash glucose monitoring in participants with impaired hypoglycemia awareness and/or recent severe hypoglycemia achieved reduced biochemical hypoglycemia only in the RT-CGM group (32).

The automated CGM-driven low glucose suspend (LGS) feature was not activated in the HypoCOMPaSS study. This is an important limitation, as greater reduction in nocturnal hypoglycemia compared to CSII and RT-CGM without LGS has been reported with sensor-augmented pumps enabling automated suspension of insulin delivery for two hours on detection of low interstitial glucose (33). Reduced severe hypoglycemia in those randomized to sensor augmented pump therapy including LGS compared to those receiving CSII alone has been reported in young people with relatively short duration type 1 diabetes (8). Access to this combination technology has recently been approved by the FDA and NICE (24).

Recovery of hypoglycemia awareness has not been reported in other trials of RT-CGM (with (7, 8) or without (30) LGS), possibly because a psycho-educational component was not included. Reversal of hypoglycemia-associated autonomic failure leading to restored awareness (34) may have required even greater reduction in time spent with low glucose levels, as absolute avoidance of biochemical hypoglycemia has not yet been attained (35). In a detailed prospective study of 11 participants with impaired awareness of hypoglycemia who used RT-CGM for >70% of the time over 18 months, questionnaire-reported hypoglycemia awareness improved with a reduction in severe hypoglycemia incidence but only a modest increase in endogenous glucose production in response to experimental hypoglycemia demonstrating that physiological counter-regulation remains impaired (36). Taken together, existing study findings underline the complex biopsychobehavioral components of hypoglycemia recognition and successful self-management (37), suggesting that reliance on RT-CGM without heightened attendance to personal cues may lead to reduced mindfulness and recognition of hypoglycemia symptoms, leading to continued high risk of severe hypoglycemia during any periods ‘off sensor’. Analysis of associations with persisting impaired awareness of hypoglycemia despite participation in the current study with its primary goal of biochemical hypoglycemia avoidance are planned.

A weakness of this study is that only 79% of participants completed full post-RCT follow-up, with only 58% completing 24-month hypoglycemia awareness Gold score. However, the baseline characteristics of those completing the study were comparable to those lost to follow-

up, and all outcomes were stable from 6 months (with much higher participant retention) through all intermediate time-points to 24 months. It could be argued that recall of severe hypoglycemia at baseline may not provide the best comparator for the data collected prospectively during the 24-month follow-up. Good correlation between retrospective and prospective recording of severe hypoglycemia over 12 months has been confirmed but with a tendency to under-reporting overall rate when relying on retrospective recall (38).

In conclusion, brief structured education in addition to informed support in active insulin dose self-adjustment underpinned by targeted self-monitoring of blood glucose leads to sustained falls in severe hypoglycemia rates in those at high risk. These should be provided, regardless of the choice of insulin delivery and glucose monitoring modality.

Acknowledgements

This research was funded by Diabetes UK. We thank the study participants and staff at Clinical Research Facilities at participating sites. In addition, we thank Prof Brian Frier (University of Edinburgh, UK) for advice on study design, Dr Pratik Choudhary (King's College London, UK) for advice on CGM analysis, and David Wilson (AHP Research) for data entry of psychosocial measures. We also thank Bayer Healthcare for providing contour glucose strips for the study duration without charge.

Funding

The study was funded by a peer-reviewed grant from Diabetes UK (07/0003556). The Research was supported by the National Institute for Health Research Newcastle Biomedical Research Centre. The National Institute for Health Research and the Cambridge National Institute for Health Research Biomedical Research Centre funded data entry and trial support.

Duality of interest

JS is a member of the Accu-Check Advisory Board (Roche Diabetes Care). Her research group (ACBRD) has received: honoraria in respect of this and her attendance at advisory board meetings for Janssen Pharmaceuticals, Medtronic and Sanofi; unrestricted educational grants from Abbott Diabetes Care, AstraZeneca and Sanofi; and sponsorship to attend educational meetings, speaker honoraria and consultancy fees from Abbott Diabetes Care, AstraZeneca, Medtronic, Novo Nordisk, Roche Diabetes Care, and Sanofi. LL has received speaker honoraria from Minimed Medtronic, Animas, Roche, Sanofi and Novo Nordisk. He has served on advisory panels for Minimed Medtronic, Animas, Roche and Novo Nordisk. MLE has received speaker honoraria from Abbott Diabetes Care, Novo Nordisk and Animas and served on advisory panels for Novo Nordisk, Abbott Diabetes Care, Medtronic, Roche and Cellnovo. SRH has served on scientific advisory boards and provided consultancy for which his institution has received remuneration from Lilly, Novo Nordisk, Takeda, Merck Sharp & Dohme and Becton Dickinson, has served as a speaker for which he received remuneration from Lilly, Novo Nordisk, Boehringer Ingelheim and Takeda and has received research support from Medtronic UK Ltd. JAMS has served on scientific advisory boards for Medtronic UK and has received travel support for attending the American Diabetes Association Annual Scientific Sessions conference from Novo Nordisk.

Author contributions

The trial was designed by the principal investigators: JAMS, JS, DK, DF, SRH and ME. SL and JS prepared the first draft of the manuscript. All authors critically reviewed and edited revisions before approving the final version. JAMS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Figure Legends

Figure 1. Severe hypoglycemia rate (Panel A) and HbA1c (Panel B) at baseline and during the 24-month study.

Annualised rate of severe hypoglycemia in the overall study population was 20 times lower during the 24-month study compared with the 12 months prior to randomization (mean±SD; *p<0.0001 using paired t-test with complete pairs only (n=96 baseline; n=69 at 24 months)) (Panel A). HbA1c reduced incrementally over the 24-month study in those with baseline HbA1c ≥8% (64 mmol/mol) and remained optimal in those with baseline HbA1c <8% (64 mmol/mol) (Panel B).

Supplemental Figure 1. Flow diagram showing number of participants allocated at random to each intervention, completing the 24-week RCT and completing 24-month follow-up.

Numbers using MDI and CSII during the RCT and post-RCT follow-up are shown. No participants randomized to SMBG commenced RT-CGM throughout the 24-month study and RT-CGM provision was not withdrawn from any participant randomized to RT-CGM (although not all continued active use, with 11 (30%) confirmed active users of this technology at study completion).

References

1. Pramming S, Thorsteinsson B, Bendtson I, Binder C. Symptomatic hypoglycaemia in 411 type 1 diabetic patients. Diabet Med. 1991;8(3):217-22.
2. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: A report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.
3. Hendrieckx C, Halliday JA, Bowden JP, Colman PG, Cohen N, Jenkins A, et al. Severe hypoglycaemia and its association with psychological well-being in Australian adults with type 1 diabetes attending specialist tertiary clinics. Diabetes Res Clin Pract. 2014;103(3):430-6.
4. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia. 2007;50:1140-7.
5. Geddes J, Schopman JE, Zammitt NN, Frier BM. Prevalence of impaired awareness of hypoglycaemia in adults with type 1 diabetes. Diabet Med. 2008;25(4):501-4.
6. Gold AE, Macleod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care. 1994;17(7):697-703.
7. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, et al. Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia. N Engl J Med. 2013;369:224-32.
8. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. J Am Med Assoc. 2013;310(12):1240-7.
9. Hopkins D, Lawrence IAN, Mansell P, Thompson G, Amiel S, Campbell M, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes the U.K. DAFNE experience. Diabetes Care. 2012;35(8):1638-42.
10. Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. Long-term effect of an education programme (HyPOS) on the incidence of severe hypoglycemia in patients with type 1 diabetes. Diabetes Care. 2010;33(3):e36: doi: 10.2337/dc09-1656.
11. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W. Blood glucose awareness training (BGAT-2): Long-term benefits. Diabetes Care. 2001;24(4):637-42.
12. Little SA, Leelarathna L, Walkinshaw E, Tan HK, Chapple O, Lubina-Solomon A, et al. Recovery of hypoglycemia awareness in long-standing type 1 diabetes: A multicenter 2 × 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). Diabetes Care. 2014;37(8):2114-22.
13. Little S, Chadwick T, Choudhary P, Brennand C, Stickland J, Barendse S, et al. Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia (the Hypo COMPaSS trial). BMC Endocr Disord. 2012;12(33):doi: 10.1186/472-6823-12-33.
14. National Institute for Health and Care Excellence. Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. NICE Technology Appraisal Guidance [TA151]. Available at: www.nice.org.uk/guidance/ta151. London: NICE; 2008.
15. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM: A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care. 1995;18(4):517-22.

16. Speight J, Barendse S, Singh H, Little SA, Inkster B, Frier BM, et al. Characterizing problematic hypoglycaemia: iterative design and preliminary psychometric validation of the Hypoglycaemia Awareness Questionnaire (HypoA-Q). Diabet Med. 2016;33(3):376-85.
17. Gonder-Frederick LA, Schmidt KM, Vajda KA, Greear ML, Singh H, Shepard JA, et al. Psychometric properties of the Hypoglycemia Fear Survey-II for adults with type 1 diabetes. Diabetes Care. 2011;34(4):801-6.
18. Bradley C. The Diabetes Treatment Satisfaction Questionnaire. In: Bradley C, editor. Handbook of Psychology and Diabetes. Switzerland: Harwood Academic Publishers; 1994.
19. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/l (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2017;40(1):155-7.
20. Yeoh E, Choudhary P, Nwokolo M, Ayis A, Amiel SA. Interventions that restore awareness of hypoglycemia in adults with type 1 diabetes: a systematic review and meta-analysis. Diabetes Care. 2015;38(8):1592-609.
21. Cox DJ, Kovatchev B, Koev D, Koeva L, Dachev S, Tcharaktchiev D, et al. Hypoglycemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe hypoglycemia among adults with type 1 diabetes mellitus. Int J Behav Med. 2004;11(4):212-8.
22. National Institute for Health and Care Excellence. Type 1 Diabetes in Adults: Diagnosis and Management. NICE Guideline [NG17]. Available at: www.nice.org.uk/guidance/ng17. London: NICE; 2015.
23. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med. 2008;25(7):765-74.
24. National Institute for Health and Care Excellence. Integrated Sensor-Augmented Pump Therapy Systems for Managing Blood Glucose Levels in Type 1 Diabetes (the MiniMed Paradigm Veo System and the Vibe and G4 PLATINUM CGM System). NICE Diagnostics Guidance [DG21]. Available at: www.nice.org.uk/guidance/dg21. London: NICE; 2016.
25. REPOSE Study Group. Relative effectiveness of insulin pump treatment over multiple daily injections and structured education during flexible intensive insulin treatment for type 1 diabetes: cluster randomised trial (REPOSE). BMJ. 2017;356(j1285):doi: 10.1136/bmj.j128.
26. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. The New England Journal of Medicine. 2008;359:1464-76.
27. de Bock M, Cooper M, Retterath A, Nicholas J, Ly T, Jones T, et al. Continuous glucose monitoring adherence: Lessons from a clinical trial to predict outpatient behavior. Journal of Diabetes Science and Technology. 2016;10(3):627-32.
28. Wong JC, Foster NC, Maahs DM, Raghinaru D, Bergenstal RM, Ahmann AJ, et al. Real-Time Continuous Glucose Monitoring Among Participants in the T1D Exchange Clinic Registry. Diabetes Care. 2014;37(10):2702-9.
29. Chamberlain J, Dopita D, Gligen E. Persistence of continuous glucose monitoring use in a community setting 1 year after purchase. Clin Diabetes. 2013;31(3):106-9.
30. van Beers CAJ, deVries JH, Kleijer SJ, Smits MM, Geelhoed-Duijvestijn PH, Kramer MHH, et al. Continuous glucose monitoring for patients with type 1 diabetes and

impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. The Lancet Diabetes and Endocrinology. 2016;4(11):893-902.
31. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet. 2016;388(10057):2254-63.
32. Reddy M, Jugnee N, El Laboudi A, Spanudakis E, Anantharanja S, Oliver N. A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with Type 1 diabetes and impaired awareness of hypoglycaemia. Diabet Med. 2017;Dec 12. doi: 10.1111/dme.13561. [Epub ahead of print].
33. Choudhary P, Shin J, Wang Y, Evans M, Hammond PJ, Kerr D, et al. Insulin pump therapy with automated insulin suspension in response to hypoglycemia. Diabetes Care. 2011;34(9):2023-5.
34. Little SA, Leelarathna L, Barendse SM, Walkinshaw E, Tan HK, Lubina Solomon A, et al. Severe hypoglycaemia in type 1 diabetes mellitus: Underlying drivers and potential strategies for successful prevention. Diabetes Metab Res Rev. 2014;30(3):175-90.
35. Youssef JEI. IN CONTROL of type 1 diabetes, despite hypoglycaemia unawareness. The Lancet Diabetes and Endocrinology. 2016;4(11):874-5.
36. Rickels MR, Peleckis AJ, Dalton-Bakes C, Naji JR, Ran NA, Nguyen HL, et al. Continuous Glucose Monitoring for Hypoglycemia Avoidance and Glucose Counterregulation in Long Standing Type 1 Diabetes. J Clin Endocrinol Metab. 2018;103(1):105-14.
37. Gonder-Frederick L, Cox D, Kovatchev B, Schlundt D, Clarke W. A biopsychobehavioral model of risk of severe hypoglycemia. Diabetes Care. 1997;20(4):661-9.
38. Pedersen-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. Diabetes Metabolism Research and Reviews. 2003;19(3):232-40.

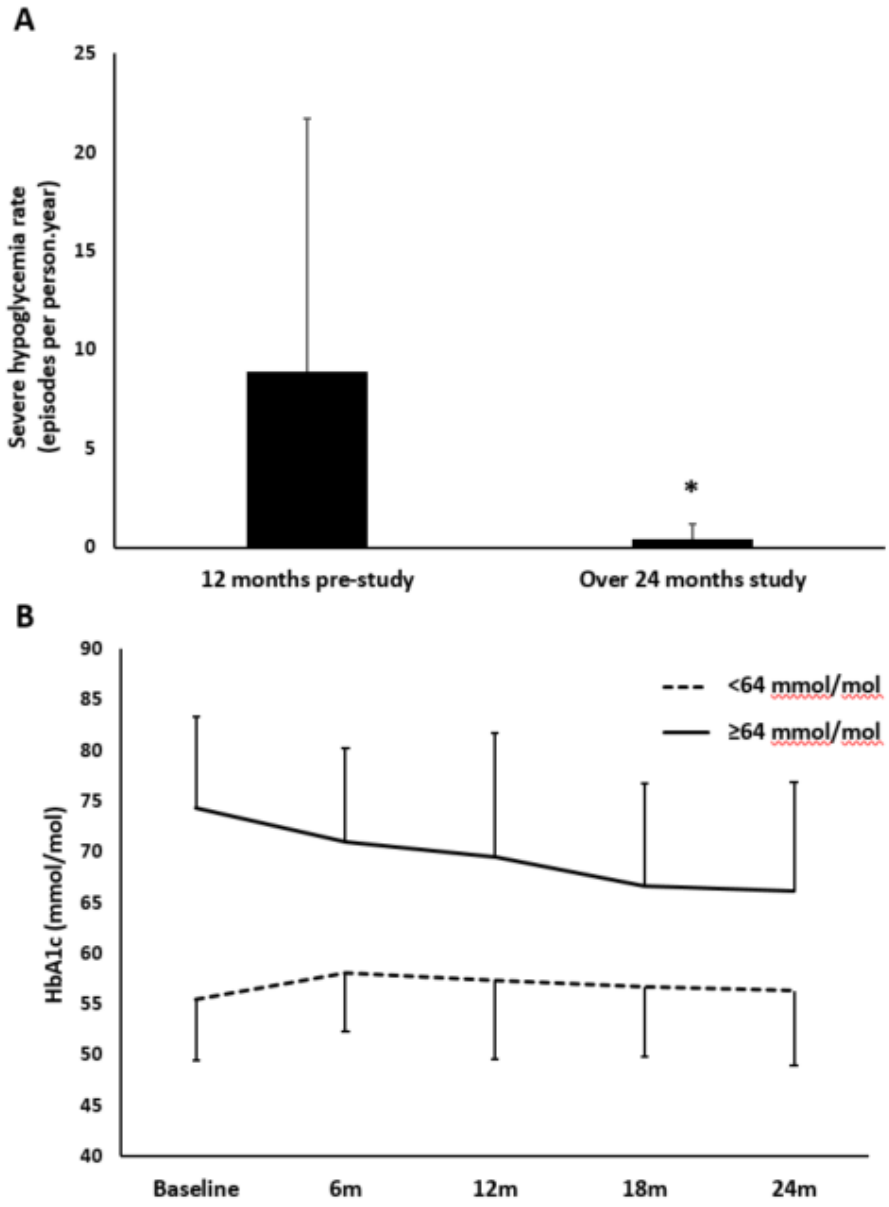


Figure 1. Severe hypoglycemia rate (Panel A) and HbA1c (Panel B) at baseline and during the 24-month study.

Annualised rate of severe hypoglycemia in the overall study population was 20 times lower during the 24-month study compared with the 12 months prior to randomization (mean±SD; *p<0.0001 using paired t-test with complete pairs only (n=96 baseline; n=69 at 24 months)) (Panel A). HbA1c reduced incrementally over the 24-month study in those with baseline HbA1c ≥8% (64 mmol/mol) and remained optimal in those with baseline HbA1c <8% (64 mmol/mol) (Panel B).

Table 1 – Baseline characteristics of participants retained at 24 months and those lost to follow-up

	Retained at 24 months (n=76)	**Lost to follow-up by month 24 (n=20)**
Age, years	49.4±12.3 (n=76)	45.5±11.4 (n=20)
Median (IQR)	50.5 (41 to 59)	46 (39 to 50.5)
Female	48 (63%) (n=76)	13 (65%) (n=20)
Diabetes duration (years)	29.2±12.6 (n=75)	27.6±11.4 (n=20)
Median (IQR)	30 (21 to 37)	25 (19.5 to 36.5)
Hypoglycemia awareness		
Gold score	5.0±1.2 (n=76)	5.2±1.0 (n=20)
Median (IQR)	5 (4 to 6)	5 (4.5 to 6)
Clarke score	5.0±1.4 (n=69)	4.7±1.9 (n=18)
Median (IQR)	5 (4 to 6)	4.5 (3 to 7)
HypoA-Q 'Impaired Awareness' scale	13.5±3.3 (n=72)	13.1±3.7 (n=20)
Median (IQR)	14 (11.5 to 16)	14 (11 to 16)
Severe hypoglycemia (12 months pre-study)		
Annualised rate per person/year	9.0±13.9 (n=76)	8.3±7.4 (n=20)
Median (IQR)	3.5 (1 to 7.5)	7.5 (2.8 to 13)
Proportion affected (n (%))	68 (89%) (n=76)	20 (100%) (n=20)
HbA1c, mmol/mol	65±11 (n=76)	70±14 (n=19)
Weight, kg	74.9±14.7 (n=76)	74.2±12.3 (n=19)
Total daily insulin dose, u/kg	0.7±0.2 (n=75)	0.6±0.2 (n=19)
Biochemical hypoglycemia, % time interstitial glucose ≤3mmol/L	3.6±4.2 (n=75)	4.2±5.2 (n=19)
Satisfaction with diabetes treatment: DTSQ		
Total satisfaction	25.4±5.5 (n=76)	23.8±6.1 (n=19)
Perceived frequency of hyperglycemia	3.7±1.4 (n=76)	3.8±1.1 (n=19)
Perceived frequency of hypoglycemia	3.8±1.2 (n=76)	3.5±1.5 (n=19)
Fear of hypoglycemia: HFS-II		
Total	55.9±25.7 (n=74)	66.9±25.1 (n=20)
Behavior	23.0±10.6 (n=74)	26.5±13.8 (n=20)
Worry	33.2±17.2 (n=76)	40.4±15.5 (n=20)

Data are mean±SD or n (%) unless stated otherwise.
Number with available data denoted by n number in parentheses.
DTSQ: Diabetes Treatment Satisfaction Questionnaire; HFS-II: Hypoglycemia Fear Survey II

Table 2 – Overall study population: hypoglycemia awareness, severe hypoglycemia, biomedical and patient-reported outcomes at baseline and every 6 months through to 24-month endpoint

	Baseline	**Month 6 (RCT endpoint)**	**Month 12**	**Month 18**	**Month 24 (Study endpoint)**	***P*-value (Baseline vs M24)**
Hypoglycemia awareness						
Gold score	5·1±1·1 (n=96)	4·1±1·6 (n=85)	3·9±1·7 (n=75)	3·5±1·8 (n=63)	3·7±1·9 (n=56)	<0·0001 (n=56)
Median (IQR)	5 (4 to 6)	4 (3 to 5)	4 (2 to 5)	3 (2 to 5)	4 (2 to 5)	
Clarke score	4·2±1·6 (n=87)	3·2±1·7 (n=80)	3·0±2·0 (n=66)	2·9±2·1 (n=61)	2·5±2·1 (n=50)	<0·0001 (n=47)
Median (IQR)	5 (4 to 6)	3 (2 to 4)	3 (1 to 5)	3 (1 to 5)	2 (0 to 4)	
HypoA-Q 'Impaired Awareness'	13·4±3·4 (n=92)	9·1±4·2 (n=84)	8·6±4·5 (n=74)	8·1±4·7 (n=65)	8·4±5·0 (n=57)	<0·0001 (n=55)
Median (IQR)	14 (11 to 16)	9.5 (6 to 12)	8.5 (5 to 12)	8 (5 to 12)	9 (4 to 11)	
Severe hypoglycemia						
Annualised rate per person/year	8·9±13·4 (n=96)	0·8±1·8 (n=90)	0·3±0·8 (n=86)	0·2±0·8 (n=73)	0·7±2·0 (n=70)	<0·0001 (n=70)
Median (IQR)	4 (2 to 7)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
Proportion affected (%)	77 (n=96)	20 (n=90)	14 (n=86)	12 (n=75)	17 (n=76)	0·02* (n=76)
HbA1c, mmol/mol	66±12 (n=95)	65±10 (n=89)	65±12 (n=74)	63±10 (n=63)	61±10 (n=72)	0·003 (n=72)
Weight, kg	74·7±14·2 (n=95)	75·3±13·6 (n=87)	75·9±13·7 (n=84)	75·1±13·7 (n=69)	75·2±13·4 (n=74)	0·93 (n=74)
Total daily insulin dose, u/kg	0·64±0·23 (n=94)	0·53±0·17 (n=87)	0·53±0·16 (n=73)	0·55±0·14 (n=50)	0·54±0·15 (n=51)	<0·0001 (n=51)
Biochemical hypoglycemia, % time interstitial glucose ≤3mmol/L	3·7±4·4 (n=94)	1·7±3·9 (n=83)	2·3±3·6 (n=55)	2·7±4·5 (n=59)	2·6±4·1 (n=55)	0·13 (n=54)
Satisfaction with diabetes treatment: DTSQ						
Total satisfaction	25·1±5·6 (n=95)	30·3±5·1 (n=84)	31·6±4·2 (n=78)	31·8±4·3 (n=65)	31·1±4·8 (n=56)	<0·0001 (n=56)
Perceived frequency of hyperglycemia	3·7±1·3 (n=95)	3·1±1·2 (n=84)	2·9±1·2 (n=78)	2·8±1·4 (n=65)	3·1±1·3 (n=57)	0·0003 (n=57)
Perceived frequency of hypoglycemia	3·7±1·3 (n=95)	2·7±1·2 (n=84)	2·7±1·1 (n=77)	2·8±1·4 (n=65)	2·7±1·3 (n=57)	0·0001 (n=57)
Fear of hypoglycemia: HFS-II						
Total	58·3±25·8 (n=94)	44·9±24·3 (n=87)	39·8±21·8 (n=60)	35·1±21·1 (n=58)	40·3±26·6 (n=47)	<0·0001 (n=46)
Behavior	23·8±11·4 (n=94)	20·4±10·1 (n=87)	20·2±10·0 (n=64)	17·1±8·6 (n=58)	19·3±11·2 (n=49)	0·001 (n=47)
Worry	34·7±17·1 (n=96)	24·4±16·5 (n=87)	20·2±15·0 (n=67)	18·4±15·2 (n=65)	21·6±17·3 (n=52)	<0·0001 (n=52)

Data are mean±SD unless stated otherwise. Number with available data denoted by n number in parentheses.
Severe hypoglycemia: Annualised rates are based on the 6 months prior to the stated time-points.
DTSQ: Diabetes Treatment Satisfaction Questionnaire; HFS II: Hypoglycemia Fear Survey II
P-values compare month 24 (endpoint) against baseline, using paired t test (complete pairs only) except *Chi squared test (complete pairs only)

Supplemental Table 1 – Hypoglycemia awareness, severe hypoglycemia, biomedical and patient-reported outcomes in MDIs vs CSII and SMBG vs RT-CGM comparisons at 24-month endpoint (ITT)

	MDI	CSII	*P*-value	SMBG	RT-CGM	*P*-value
Hypoglycemia awareness						
Gold score	3·5±1·7 (n=29)	3·9±2·1 (n=27)	0·35	3·8±2·0 (n=28)	3·5±1·8 (n=28)	0·57
Median (IQR)	3 (2-4)	4 (2-6)		4 (2-5.5)	3 (2-5)	
Clarke score	2·3±2·3 (n=26)	2·8±1·9 (n=24)	0·39	2·7±2·2 (n=25)	2·3±2·0 (n=25)	0·51
Median (IQR)	1 (0-4)	3 (1.5-4.5)		3 (0-5)	2 (1-4)	
HypoA-Q 'Impaired Awareness' scale	7·6±5·0 (n=29)	9·2±5·0 (n=28)	0·24	8·3±5·0 (n=29)	8·4±5·1 (n=28)	0·90
Median (IQR)	8 (3-11)	9.5 (4.5-12)		9 (4-11)	8.5 (3.5-12)	
Severe hypoglycemia						
Annualized rate over 24-month follow-up, per person/year	0·4±0·8 (n=34)	0·4±0·9 (n=35)	0·97	0·5±1·0 (n=35)	0·3±0·6 (n=34)	0·33
Median (IQR)	0 (0-0.5)	0 (0-0.5)		0 (0-0.5)	0 (0-0.5)	
Proportion affected, %	40 (n=40)	32 (n=38)	0·44*	32 (n=38)	40 (n=40)	0·44*
HbA1c, mmol/mol	62±12 (n=37)	61±9 (n=35)	0·87	61±11 (n=36)	61±10 (n=36)	
Weight, kg	75·2±12·7 (n=39)	75·2±14·3 (n=35)	0·99	75·1±13·7 (n=39)	75·4±13·2 (n=35)	0·93
Total daily insulin dose, u/kg	0·56±0·17 (n=25)	0·51±0·14 (n=26)	0·27	0·52±0·12 (n=27)	0·56±0·18 (n=24)	0·27
Biochemical hypoglycemia, % time interstitial glucose ≤3mmol/L	2·4±3·8 (n=30)	2·8±4·5 (n=25)	0·72	2·6±3·6 (n=27)	2·6±4·6 (n=28)	0·98
Satisfaction with diabetes treatment: DTSQ						
Total satisfaction	30·7±5·0 (n=29)	31·7±4·6 (n=27)	0·43	31·0±4·8 (n=31)	31·3±4·8 (n=25)	0·81
Perceived frequency of hyperglycemia	2·9±1·3 (n=29)	3·2±1·4 (n=28)	0·40	3·0±1·3 (n=31)	3·2±1·4 (n=26)	0·61
Perceived frequency of hypoglycemia	2·4±1·3 (n=29)	3·0±1·3 (n=28)	0·09	2·8±1·3 (n=31)	2·6±1·4 (n=26)	0·66
Fear of hypoglycemia: HFS-II						
Total	38·3±26·2 (n=23)	42·2±27·3 (n=24)	0·62	40·5±24·9 (n=24)	40·0±28·8 (n=23)	0·95
Behavior	18·3±10·6 (n=24)	20·4±11·8 (n=25)	0·52	18·7±8·9 (n=26)	20·0±13·5 (n=23)	0·68
Worry	20·6±17·5 (n=25)	22·6±17·3 (n=27)	0·69	23·1±1·.3 (n=27)	20·0±17·5 (n=25)	0·52

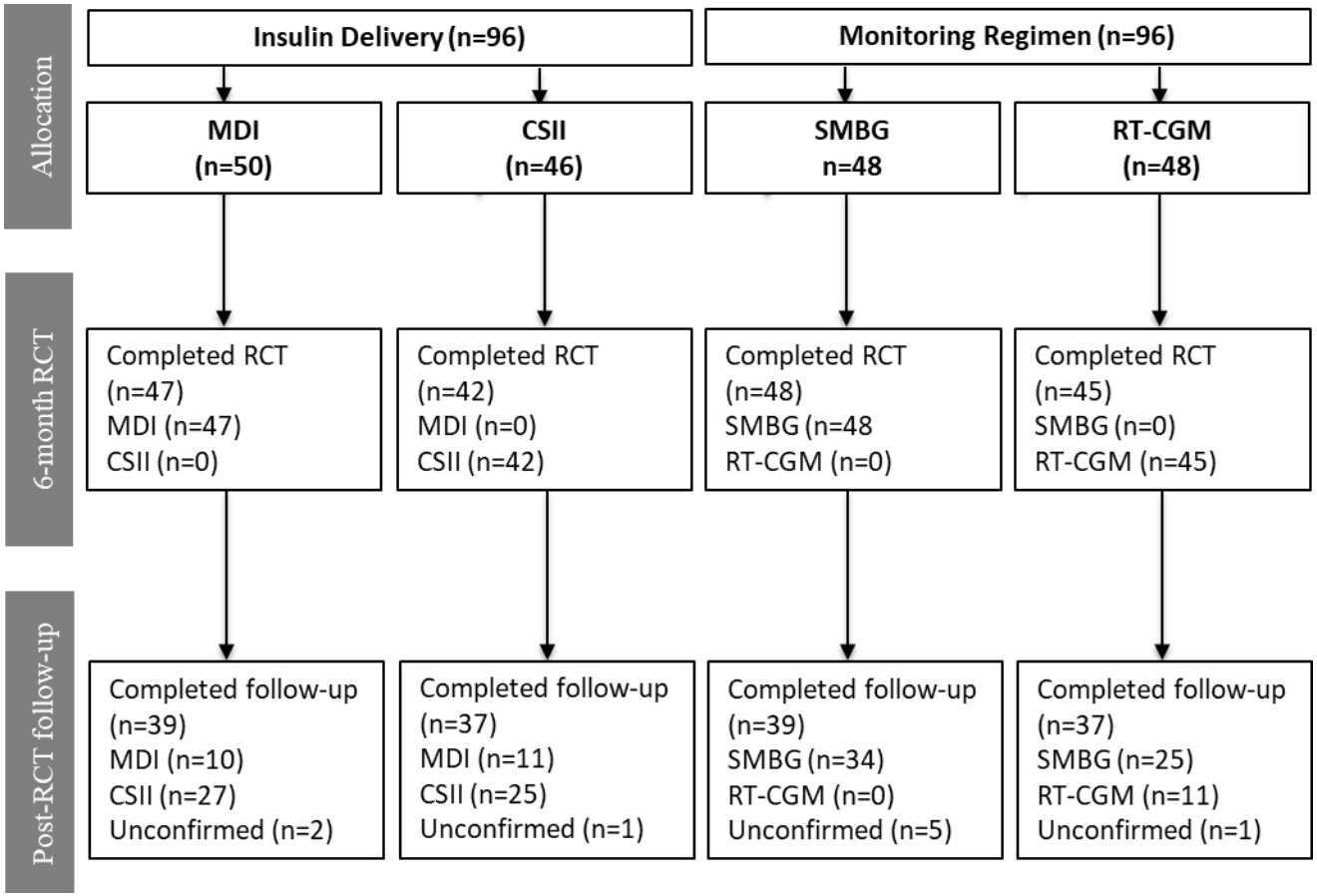
Data are mean±SD unless stated otherwise. Number with available data denoted by n number in parentheses.

P-values compare MDI and CSII groups at month 24, using two-sample t test, except *X^2 test.

Supplemental Table 2 – Hypoglycemia awareness, severe hypoglycemia, biomedical and patient-reported outcomes at 24-month endpoint (per protocol): insulin delivery modality (MDI only vs. CSII only vs. switched) and RT-CGM use (<50% of time vs ≥50% of time)

	Insulin delivery modality throughout 24-month study (n=80)			**RT-CGM use (n=14)**	
	MDI only (n=10)	**Switched (MDI & CSII) (n=45)**	**CSII only (n=25)**	**<50% time (n=6)**	**≥50% time (n=8)**
Hypoglycemia awareness					
Gold score	2·9±1·2 (n=8)	3·6±1·9 (n=28)	3·9±2·1 (n=18)	2·8±1·9 (n=5)	3·3±2·0 (n=7)
Median (IQR)	3 (2-3.5)	4 (2-5)	4 (2-6)	2 (2-3)	3 (2-4)
Clarke score	1·4±1·9 (n=7)	2·5±2·0 (n=25)	2·8±2·2 (n=16)	1·0±1·4 (n=5)	1·8±1·7 (n=6)
Median (IQR)	1 (0-3)	3 (1-4)	2 (0.5-5)	0 (0-2)	1.5 (1-2)
HypoA-Q 'Impaired Awareness'	6·6±3·5 (n=8)	7·9±5·2 (n=27)	9·2±5·2 (n=20)	4·2±2·2 (n=5)	7·7±5·7 (n=7)
Median (IQR)	6 (3.5-10)	9 (3-11.5)	9.5 (4-11.5)	3 (3-6)	5 (3-13)
Severe hypoglycemia					
Annual rate over 24-month follow-up, per person/year	0·2±0·5 (n=10)	0·4±0·8 (n=33)	0·5±1·0 (n=25)	0·0±0·0 (n=6)	0·3±0·4 (n=8)
Median (IQR)	0 (0-0.5)	0 (0-0)	0 (0-0.5)	0 (0-0)	0 (0-0.5)
Proportion affected, %	30 (n=10)	36 (n=39)	32 (n=25)	0 (n=6)	38 (n=8)
HbA1c, mmol/mol	66±13 (n=9)	62±11 (n=38)	59±8 (n=23)	57±7(n=6)	56±9 (n=8)
Weight, kg	79·0±11·6 (n=10)	75·0±13·7 (n=37)	73·8±14·2 (n=24)	73·9±13·8 (n=6)	79·9±14·3 (n=8)
Total daily insulin dose, u/kg	Data not collected	0·55±0·16 (n=30)	0·52±0·15 (n=20)	0·58±0·16 (n=5)	0·66±0·13 (n=5)
Biochemical hypoglycemia, % time interstitial glucose ≤3mmol/L	2·8±4·8 (n=10)	2·8±4·7 (n=25)	2·3±3·0 (n=18)	4·3±8·8 (n=5)	3·0±4·8 (n=6)
Satisfaction with diabetes treatment: DTSQ					
Total satisfaction	30·1±2·9 (n=7)	30·8±6·0 (n=28)	31·9±3·4 (n=19)	31·2±4·4 (n=5)	31·2±5·0 (n=6)
Perceived frequency of hyperglycemia	2·3±0·8 (n=7)	3·3±1·4 (n=29)	3·1±1·4 (n=19)	3·2±1·9 (n=5)	3·5±1·0 (n=6)
Perceived frequency of hypoglycemia	2·1±1·2 (n=7)	2·6±1·5 (n=29)	3·2±1·1 (n=19)	2·4±1·3 (n=5)	2·8±1·3 (n=6)
Fear of hypoglycemia: HFS-II					
Total	31·8±15·7 (n=6)	43·7±29·9 (n=23)	39·8±25·7 (n=17)	24·5±12·1 (n=4)	28·1±17·4 (n=7)
Behavior	18·3±5·9 (n=6)	18·8±12·4 (n=24)	20·7±11·4 (n=18)	15·3±6·3 (n=4)	16·4±9·0 (n=7)
Worry	13·5±11·2 (n=6)	26·0±19·4 (n=25)	19·1±15·5 (n=19)	15·0±15·4 (n=5)	11·7±10·1 (n=7)

Data are mean±SD unless stated otherwise. Number with available data denoted by n number in parentheses.
No formal hypothesis testing was performed due to small numbers of observations in certain groups.
Complete RT-CGM usage data were available for 14 of the 17 participants who continued to use RT-CGM.



Supplemental Figure 1. Flow diagram showing number of participants allocated at random to each intervention, completing the 24-week RCT and completing 24-month follow-up.

Numbers using MDI and CSII during the RCT and post-RCT follow-up are shown. No participants randomized to SMBG commenced RT-CGM throughout the 24-month study and RT-CGM provision was not withdrawn from any participant randomized to RT-CGM (although not all continued active use, with 11 (30%) confirmed active users of this technology at study completion).